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Oxytocin, motherhood and bonding

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Release of the peptide hormone oxytocin in the brain has been shown to influence both maternal, sexual and social bonding behaviours although there are a number of species differences. This review summarizes findings on the distributions of oxytocin and oxytocin receptors in the brain, together with factors governing their expression, release of the peptide in the brain and its behavioural actions. A model of how oxytocin may act to alter maternal and socio-sexual behaviours is proposed which initially involves activation of oxytocin neurones in a single brain site, the paraventricular nucleus of the hypothalamus (PVN), following vaginal and cervical stimulation. This causes a co-ordinated release of the peptide in the PVN and its terminal projection regions for up to 1 h and this promotes different behavioural components, primarily through modulation of classical transmitter systems. *Experimental Physiology* (2000) **85S**, 111*S*–124*S*.

While the role of oxytocin in parturition and milk ejection has been established for a considerable time, the potential for its release within the brain to influence behaviour was not demonstrated until 1979 when it was shown to induce maternal behaviour in non-pregnant rats (Pedersen & Prange, 1979). It was not until 1986, however, that detailed evidence was produced in sheep that brain oxytocin levels are elevated by vagino-cervical stimulation occurring at the time of birth (Kendrick *et al.* 1986). Since that time the peptide has also been associated with influences on social, sexual and aggressive behaviours and even in memory function (Table 1). This review will consider how oxytocin acts to produce such behavioural effects, concentrating mainly on maternal and social bonding actions where most experimental data exist.

Neuroanatomical localization of oxytocin and its receptors

Immunocytochemistry and *in situ* hybridization histochemistry have revealed that the distribution of cells and processes containing oxytocin immunoreactivity or mRNA is broadly similar in many species (Sofroniew, 1983; Broad *et al.* 1993*a*; Crowley *et al.* 1995).

The major source of oxytocin neurones that project within the brain is the hypothalamic paraventricular nucleus (PVN).

There is similar agreement across species about the regions that contain cells expressing oxytocin receptor mRNA (Yoshimura *et al.* 1993; Broad *et al.* 1999), although this has only become established with the cloning and sequencing of the receptor gene, allowing mRNA expression to be detected. Studies using ligand binding have not always been successful in demonstrating the presence of these receptors in some species (Lévy *et al.* 1992*a*; Tolockzo *et al.* 1997). Recent studies quantifying changes in mRNA expression or protein have overcome this problem and indicated that distribution within the brain is far more extensive than originally thought (Broad *et al.* 1999; Table 2). There is a remarkable concordance between brain sites showing increased c-*fos* mRNA expression (used as an activity-dependent marker) following the induction of maternal behaviour and those containing oxytocinergic cells, processes and receptors (da Costa *et al.* 1997; Kendrick *et al.* 1997*a*; Table 2). This is also the case for structures important in mediating social and sexual behaviours and social recognition/bonding based on olfactory cues (Flanagan *et al.* 1993; da Costa *et al.* 1997).

Factors which influence the potential for an animal to show maternal or socio-sexual behaviours also impact on the levels of oxytocin and oxytocin receptor expression in a number of different species. Thus, levels of oxytocin immunoreactivity, mRNA expression and receptor mRNA expression are altered in many regions associated with maternal behaviour at the time of parturition, during lactation and following exogenous treatments with oestrogen and progesterone (Burbach & Adan, 1990; Insel & Shapiro, 1992; Schumacher *et al.* 1992; Broad *et al.* 1993*a*; Crowley *et al.* 1995; Zingg *et al.* 1995). Similarly, differential levels of oxytocin receptor expression are seen in the bed nucleus of the stria terminalis, lateral septum and nucleus accumbens in mouse and vole strains depending upon whether they have a social/monogamous disposition or an asocial/promiscuous one (Insel *et al.* 1991; Insel & Shapiro, 1992). These regions are known to be important for social behaviours and their associated rewards.

In rats, oxytocinergic cells do not have large numbers of oestrogen receptors (Burbach *et al.* 1995) and of these only the β-type is expressed (Patisaul *et al.* 1999). Also, although the rat oxytocin gene does have a putative oestrogen responsive element, it is imperfect (Burbach & Adan, 1990) and does not

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appear to have an important role *in vivo*. Indeed in sheep, upregulation of mRNAs for both oxytocin (Broad *et al.* 1993*a*) and its receptor (Broad *et al.* 1999) in PVN cells as a result of pregnancy is not entirely mimicked by oestrogen and progesterone treatment. Therefore other factors, such as glucocorticoids or thyroid hormone, may contribute to the stimulation of the oxytocin peptide and receptor genes (Adan *et al.* 1993).

Another important factor that influences levels of oxytocin receptor mRNA expression is maternal experience. In sheep, nulliparous ewes are known to have more problems in developing post-partum maternal responses than multiparous ones. The level of birth-induced upregulation of oxytocin receptor mRNA in the PVN of primiparous ewes is significantly less than that seen in multiparous ones (Broad *et al.* 1999). Interestingly, work in rats has also shown that maternal experience can induce permanent morphological changes in oxytocinergic neurones (Hatton *et al.* 1992).

As already discussed, c-*fos* expression is increased in oxytocinergic cells at the time of birth when oxytocin and its receptor are also upregulated. Mutant mice lacking the *fos*-b gene, another member of the Fos family, show defective nursing behaviour (Brown *et al.* 1996). We have recently shown that c-*fos*/c-*jun* antisense infusions into the PVN prevent upregulation of oxytocin expression at birth and impair oxytocin release and some aspects of maternal behaviour (da Costa *et al.* 1999). Thus this immediate early gene family may exert an important transcriptional control over the expression of the oxytocin gene in the PVN.

Oxytocin and maternal behaviour

Behavioural effects of oxytocin and oxytocin antagonists

It was first demonstrated in rats that intracerebroventricular (I.C.V.) infusions of oxytocin can induce short-latency (< 30 min) maternal responses in hormone-primed virgin animals (Pedersen & Prange, 1979; Pedersen *et al.* 1982; Fahrbach *et al.* 1985*a*). Infusions of the related peptide vasopressin were considerably less effective in this respect. Later experiments showed that I.C.V. infusions of oxytocin antagonists (van Leengoed *et al.* 1987; Fahrbach *et al.* 1985*b*) or antisera (Pedersen *et al.* 1985) could prevent these actions of oxytocin, and could also delay the onset of post-partum maternal behaviour. This led to the attractive hypothesis that oxytocin could have complementary actions in terms of its peripheral and central actions. On the one hand it could promote uterine contractions and milk let-down peripherally, and promote maternal responsiveness by acting centrally. Similar complementary peripheral and central actions have been claimed for other peptides such as angiotensin, cholecystokinin, corticotropin-releasing hormone, luteinizing hormone-releasing hormone and vasopressin. However, while similar effects of I.C.V. infusions were later reported in mice (McCarthy, 1990), the precise importance of central oxytocin release in maternal behaviour induction in rodents has been called into question. Thus some groups failed to find any effects of I.C.V. oxytocin in rats (Rubin *et al.* 1983; Bolwerk & Swanson, 1984) or could only obtain them in anosmic animals or animals in novel environments (Wamboldt & Insel, 1987). The most recent negative evidence comes from mice with a targeted mutation of the oxytocin gene which have no reported dysfunction in maternal behaviour (Nishimori *et al.* 1996; Young *et al.* 1997).

These varied findings in both rats and mice are perhaps not that suprising in view of the fact that oxytocin infusions do not mimic the speed of induction of maternal behaviour seen post-partum (i.e. it takes > 30 min for I.C.V. infusions of oxytocin to have behavioural effects whereas these behaviours are induced immediately post-partum). Further, the mouse strain used to make the oxytocin gene knockout (C57Bl6) is almost spontaneously maternal when presented with pups (Young *et al.* 1997). Indeed, in both mice and rats the mere presence of pups reliably evokes maternal responses after treatments with sex hormones, and is independent of the process of actually giving birth. Thus, if brain oxytocin release plays a role in the control of maternal behaviour in these species, it is a facilitatory rather than an essential one.

One other point that is clear from rodent studies is that if the main source of brain oxytocin projections, the PVN, is damaged then post-partum induction of maternal behaviour is delayed, but once maternal behaviour is established then damage to this region does not interfere with it. This has been shown both using lesions in rats (Insel & Harbaugh, 1989) and indirectly in mice mutant for the imprinted gene PEG3, where deficits in post-partum maternal behaviour induction are correlated with significant cell loss in the PVN (Li *et al.* 1999).

In sheep, evidence suggests that oxytocin plays a much greater role in post-partum induction of maternal responses. Intracerebroventricular oxytocin infusions can induce full maternal responses in < 30 s in non-pregnant animals, provided that they are oestrogen-primed (Kendrick *et al.* 1987). None of the oxytocin receptor antagonist ligands used to block oxytocin effects in rodents have proved to be effective in sheep and indeed cannot be used to demonstrate receptor binding in sheep brain (although they do bind in the kidney) (Lévy *et al.* 1992*a*). However, oxytocin actions can be partially blocked by infusions of the cyclic hexapeptide receptor antagonist L-366,670 (Fig. 1). The oxytocin receptor agonist $\text{Thr}^4,\text{Gly}^7$-oxytocin is just as potent as oxytocin in stimulating maternal behaviour. Similar infusions of up to 50 μg of vasopressin have no significant effect.

In sheep, maternal experience also influences responsivity to oxytocin, as would be predicted from findings on oxytocin receptor mRNA expression. Thus, with short-term progesterone and oestrogen priming, I.C.V. oxytocin fails to reliably induce full maternal behaviour in nulliparous ewes but is effective in multiparous ones (Keverne & Kendrick, 1991). However, in nulliparous animals exposed to long-term combined sex steroid treatment (i.e. 6–8 weeks, which is sufficient to stimulate lactation; Kendrick *et al.* 1992*a*), I.C.V. oxytocin is effective in stimulating full maternal behaviour (K. M. Kendrick, unpublished observations). Similarly in primiparous ewes prevented from becoming maternal at birth by using an epidural anaesthetic block, I.C.V. oxytocin treatment was also effective in inducing full maternal responsiveness (Lévy *et al.* 1992*b*).

While no direct evidence linking central oxytocin to human maternal behaviour exists, concentrations of the peptide are increased in the mother's cerebrospinal fluid at birth (Takagi *et al.* 1985) and post-partum levels of positive social feelings and reduced anxiety are correlated with elevated plasma concentrations. These behavioural factors are also enhanced in women delivered normally as opposed to by Caesarean section (Nissen *et al.* 1998). The only study carried out on non-human primates has also reported an increase in affiliative and some maternal behaviour components in rhesus monkeys following I.C.V. infusions (Holman & Goy, 1995).

Effects of oxytocin on social and bonding behaviours

Unlike rats and mice, sheep selectively bond with their individual offspring within 2 h of giving birth. This selectivity is based on the mother being able to form an olfactory memory allowing her to distinguish uniquely each of her lambs from all others. Interestingly, human mothers are also able to selectively recognize the smell of their own infants within 30 min of birth (Porter *et al.* 1983). The behavioural evidence that a bond has formed in sheep is that the mother will reject all lambs other than their own. Both oxytocin immunoreactivity and oxytocin receptor mRNA expression increase in the granule cell layer of the olfactory bulb, which is a key site of plasticity changes underlying the formation of olfactory memory (Kendrick *et al.* 1992*b*, 1997*b*). We have also confirmed that hormone-primed animals given I.C.V. oxytocin infusions all bond selectively with their lambs in 2–4 h (Fig. 1). Thus, in sheep, oxytocin is probably involved in stimulating both maternal behaviour and facilitating the formation of olfactory recognition associated with the maternal bond.

Oxytocin infusions can also facilitate short-term social recognition in rats, and oxytocin antagonists can block this action (Dluzen *et al.* 1998; Engelman *et al.* 1998). Recent work on male mice, null-mutant for the oxytocin gene, has similarly shown that they are impaired on such social recognition tasks (Winslow *et al.* 1998).

The most compelling evidence for the role of brain oxytocin in social behaviour and bonding comes from work on voles. In female prairie voles, which form long-term exclusive pair-bonds with their male partners following mating, I.C.V. oxytocin infusions will promote the formation of these bonds independently of mating (see Insel, 1992, 1997; Carter *et al.* 1995; Carter, 1998; Young *et al.* 1998). Interestingly, similar infusions into males (which also bond with their female partner after mating) do not promote bonding. Instead, vasopressin infusions promote bonding in the male but have no comparable effect in the female. Thus there is an intriguing sex difference in oxytocin and vasopressin actions of male and female bonding behaviour, even though there are no large sex differences in oxytocin or oxytocin receptor distributions in the brain (Insel & Hulihan, 1995). However, differential receptor densities do appear to play a role within sexes since neither vasopressin nor oxytocin infusions can induce social bonding in asocial, promiscuous species of vole which have altered levels of expression in the lateral septum, bed nucleus of the stria terminalis and nucleus accumbens (Insel 1992; 1997; Young *et al.* 1998).

Effects of oxytocin on sexual behaviour

Compared with the slightly conflicting evidence for a role of brain oxytocin in rodent maternal behaviour, its influence on female sexual behaviour in rats and hamsters is much stronger (see Witt, 1995; Whitman & Albers, 1995). Thus, I.C.V. infusions, or infusions directly into the medial preoptic area or the ventromedial hypothalamus, promote lordosis behaviour in sex hormone-primed animals. Similarly, infusions of oxytocin antagonists can prevent lordosis induction. In both of these species oxytocin receptor levels are increased by oestrogen treatment. However, in mice mutant for the oxytocin gene, no

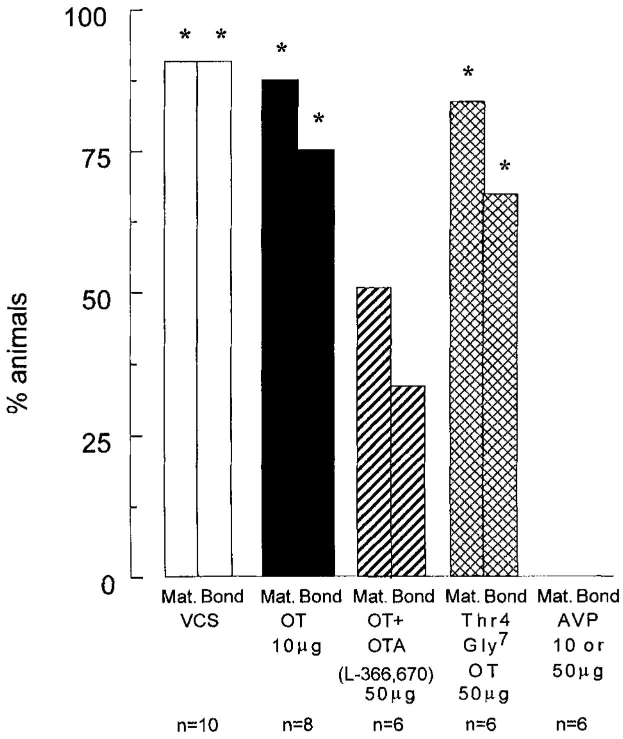

Figure 1

Histograms show the percentage of animals showing full maternal behaviour (Mat.) and selective bonding (within 4 h; Bond) following long-term oestradiol and progesterone treatment, sufficient to induce lactation, and I.C.V. infusions of oxytocin (OT), oxytocin agonist (Thr^4,Gly^7-OT) and antagonist (OTA, L-366,670) and vasopressin (AVP). In each treatment group, each animal acted as its own control, having received a saline infusion first. $*P < 0.05$ *vs.* control (binomial test). To allow I.C.V infusions to be made, all animals were first surgically prepared with unilateral guide tubes under general anaesthesia (halothane) and with full sterile precautions as previously described (Kendrick *et al.* 1987). VCS, vagino-cervical stimulation.

deficits in female sexual behaviour occur (Nishimori *et al.* 1996; Young *et al.* 1997), although this species shows decreased oxytocin receptor levels in the ventromedial nucleus following sex-steroid treatment (Insel *et al.* 1993). The situation is further complicated by the fact that in female prairie voles (Witt, 1995) and sheep (Kendrick *et al.* 1993) brain oxytocin infusions actually inhibit sexual receptivity. Indeed, in sheep, receipt of multiple intromissions from males also inhibits sexual receptivity, while vaginal stimulation promotes oxytocin release in the ventromedial nucleus (Kendrick *et al.* 1993).

Whether oxytocin facilitates or inhibits female sexual behaviour may reflect differential sex hormone priming conditions that promote behavioural oestrus across species. Thus in rats and hamsters, progesterone is used to induce receptivity following a period of oestrogen priming. In rats, this progesterone treatment is known to promote oxytocin release (Caldwell *et al.* 1992). In voles and sheep, oestrogen is used to induce receptivity following progesterone treatment and progesterone *per se* is actually inhibitory to it (Kendrick *et al.* 1993; Witt, 1995). Thus, in these latter species oxytocin acts to inhibit receptivity. Indeed, in sheep this makes sense since if the same peptide simultaneously facilitated sexual and maternal behaviours at birth it could generate a difficult conflict of interest.

Work on male rats has also shown actions of brain oxytocin on male erection and sexual behaviour (see Witt, 1995). Effects on sexual behaviour appear to be dose dependent, with low doses facilitating the behaviour and high doses depressing it. Indeed effects produced by high doses appear to be similar to the quiescent behaviour shown during the post-ejaculatory interval. Once again, however, the general importance of brain oxytocin for male sexual behaviour has been called into question by observations in mice mutant for the oxytocin gene which show normal behaviour in this respect (Nishimori *et al.* 1996; Young *et al.* 1997).

Release of oxytocin in the brain

In sheep, oxytocin concentrations are greatly increased in the cerebrospinal fluid (CSF) post-partum (Kendrick *et al.* 1986), but not in animals that have an epidural anaesthetic block in place and do not show post-partum induction of maternal behaviour (Lévy *et al.* 1992*b*). These high CSF levels of oxytocin are not derived from the blood since < 0.01 % of the peptide is able to cross the blood–brain barrier (Kendrick *et al.* 1986). In humans, CSF oxytocin concentrations also increase during normal labour in women (Takagi *et al.* 1985).

To elucidate the specific sites of oxytocin release, a number of studies in rats and sheep have used *in vivo* microdialysis sampling techniques. To date these have shown that oxytocin levels increase in the bed nucleus of the stria terminalis (Kendrick *et al.* 1992*a*), hippocampus (Landgraf *et al.* 1991), medial preoptic area (Kendrick *et al.* 1992*a*), mediobasal hypothalamus (Kendrick *et al.* 1993), olfactory bulb (Kendrick *et al.* 1988*a*,*b*; Lévy *et al.* 1995), PVN (Neumann *et al.* 1993; da Costa *et al.* 1996), septum (Landgraf *et al.* 1991), area of the substantia nigra (Kendrick *et al.* 1988*a*) and the supraoptic nucleus (Neumann *et al.* 1993) at birth and/or in response to vagino-cervical stimulation (see Table 3). Indeed, since the PVN is the main source of oxytocinergic projections in the brain, one would predict that oxytocin release occurs in the majority, if not all, of its terminal regions.

Actions of oxytocin released in different neural substrates

The proposed actions of oxytocin released in different brain regions are summarized in Fig. 2 in relation to maternal behaviour.

Behavioural effects of PVN infusions

We hypothesized that for oxytocin to induce full maternal behaviour, it was likely that its release would need to occur simultaneously in many different terminal regions. Since the PVN itself has oxytocin autoreceptors, and oxytocin is known to promote increased activity of oxytocinergic neurones in this region (Moos *et al.* 1984; Freund-Mercier *et al.* 1993; da Costa *et al.* 1996), direct infusions of oxytocin into the PVN should stimulate release in all its terminal regions. Using bilateral retrodialysis infusions in sheep, we confirmed that increasing oxytocin concentrations bilaterally in the region of the PVN did indeed induce full maternal responses in oestrogen- and progesterone-treated animals (da Costa *et al.* 1996). This effect could be mimicked by the ring structure of the peptide alone (tocinoic acid) and occurred at doses approximately 150-fold lower than those required to produce similar actions following I.C.V. infusions. As with I.C.V. treatment, direct infusions of vasopressin into the PVN did not reliably induce maternal behaviour.

While it might be concluded from the above studies that the PVN itself is the critical site for controlling maternal responses this is clearly not the case. Thus, in rodents, the PVN is not essential for the maintenance of maternal behaviour once it has been induced (Insel & Harbaugh, 1989), and therefore it is unlikely that this region plays a specific functional role other than as a co-ordinator.

Behavioural effects of oxytocin infusions into terminal regions

If co-ordinated release of oxytocin is required in a number of different terminal regions for complete maternal behaviour to be stimulated, one would predict that infusions into specific terminal regions would only affect specific components of maternal behaviour. This was confirmed by further studies on sheep where direct oxytocin infusions into the medial preoptic area and olfactory bulb only reduced one component, namely aggression towards lambs (Kendrick *et al.* 1997*a*). This suggests that the olfactory projection from the main olfactory bulb via the amygdala and stria terminalis to the medial preoptic area may play a role in mediating odour-evoked aggressive responses towards lambs and that oxytocin inhibits this response. It may also reduce olfactory-mediated aversive responses to amniotic fluid odours (Lévy & Poindron, 1987). Similarly in the rat, interfering with olfactory processing may promote maternal responses by reducing aversive responses to pup odours (Fleming *et al.* 1979). Indeed, one study has claimed that short-latency maternal behaviour can be induced in some animals by direct oxytocin infusions into the olfactory bulb itself (Yu *et al.* 1996*a*,*b*).

Other behavioural components associated with maternal behaviour and bonding may also result from actions of oxytocin on specific neural substrates. Thus in sheep, oxytocin infusions into the mediobasal hypothalamus inhibit sexual receptivity (Kendrick *et al.* 1993) and this may partly explain why these animals are not sexually receptive immediately post-partum, in spite of experiencing a similar priming regime of sex hormones in late pregnancy to that at oestrus. In male rats, oxytocin infusions into the olfactory bulbs and hippocampus have been reported to facilitate olfactory social recognition memory (Dluzen *et al.* 1998; Engelman *et al.* 1998). In both sheep and voles this development of olfactory recognition is an essential requirement for social bonding to occur.

In rats, several studies have also reported effects of direct infusions of oxytocin or oxytocin antagonists into a number of brain regions. A preliminary report showed facilitation of maternal behaviour by a large dose (200 ng) of oxytocin in the ventral tegmentum but not the medial preoptic area or medial amygdala (Fahrbach *et al.* 1995*a*). However, since this dose was the same as that known to be effective when given I.C.V., it is questionable whether the ventral tegmentum is specifically involved. More recently, infusions of an oxytocin antagonist into the medial preoptic area and ventral tegmentum have been reported to block post-partum activation of maternal behaviour (Pedersen *et al.* 1994). However, this is still consistent with the hypothesis that oxytocin release must be effective in all terminal regions simultaneously for full

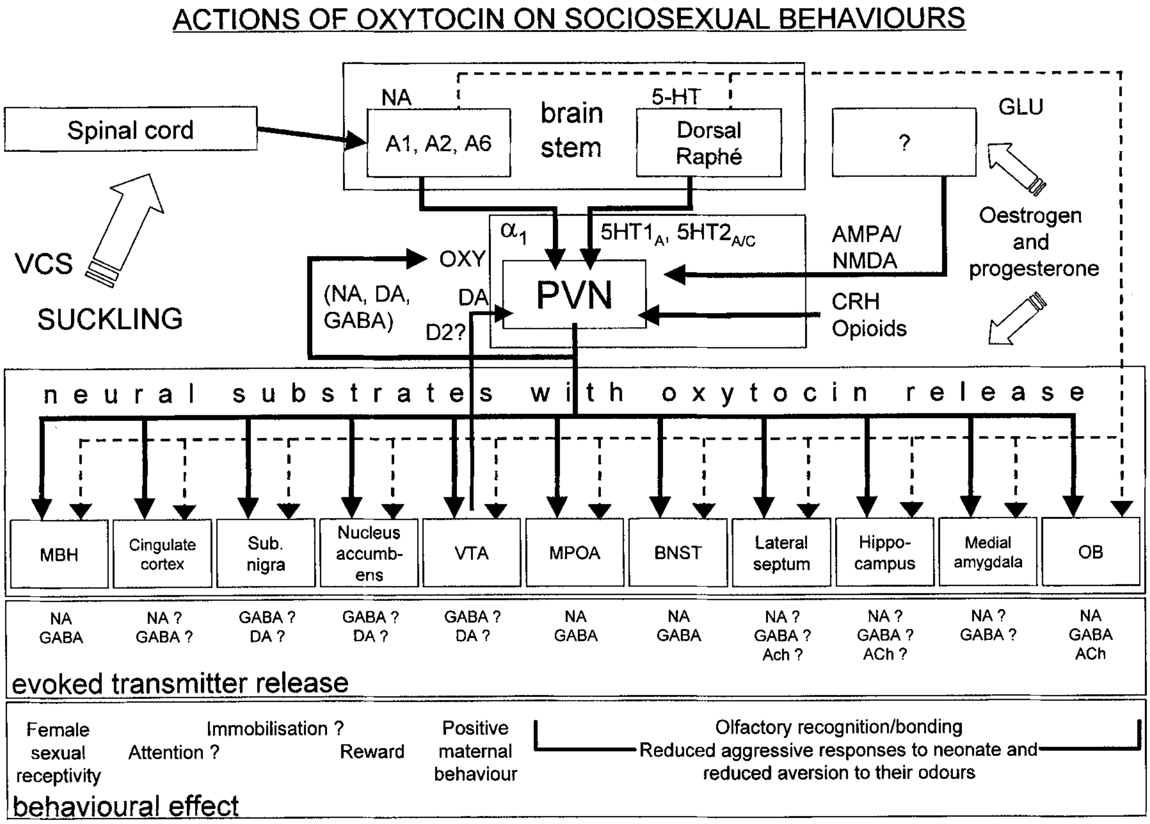

Figure 2

Schematic diagram showing sites of oxytocin release involved in mediating altered maternal and socio-sexual behaviours. Vaginocervical stimulation (VCS) stimulates parvocellular oxytocinergic cells in the paraventricular nucleus (PVN) via noradrenergic (NA; A1, A2, A6), 5-HT (dorsal raphé), dopaminergic (DA, ventral tegmentum, VTA) and glutamatergic (GLU) projections. The receptors activated by these classical transmitters are also indicated (α_1; 5HT1$_A$, 5HT2$_{A/C}$; D2; AMPA, NMDA, respectively). The schematic diagram also shows that these diffuse projection systems can influence oxytocin terminal regions independently of the PVN. As a result of PVN activation, oxytocin is released at the terminal sites indicated and within these sites modulates noradrenaline (NA), dopamine (DA), acetylcholine (ACh) and GABA release (depending upon the site). The proposed behavioural effect of oxytocin release in its various terminal sites is then given. Modulatory actions of oxytocin (OXY), corticotropin releasing hormone (CRH) and opioids are indicated at the level of the PVN and of oestrogen and progesterone in the PVN and terminal regions. ? indicates proposed actions for which no experimental evidence has been produced. MBH, mediobasal hypothalamus; Sub. nigra, substantia nigra; MPOA, medial preoptic area; BNST, bed nucleus of the stria terminalis; OB, olfactory bulb.

Table 1. Actions of oxytocin on socio-sexual behaviours

	Species			
Behaviours	**Rat**	**Mouse**	**Prairie vole**	**Sheep**
Maternal behaviour	↑	↑	?	↑↑↑
Paternal behaviour	-	-	←→	-
Male sexual behaviour	↑↑ or ↓	←→	↓↓	?
Female sexual behaviour	↑↑↑	←→	↓↓	↓
Male affiliative behaviour	↑↑	←→	←→ or ↑	?
Female affiliative behaviour	?	←→	↑↑↑	↑↑
Autogrooming	↑↑	↑↑	?	-
Social recognition memory	↑↑	↑↑	↑↑	↑↑
Olfactory investigation	↑↑	↑↑	↑↑	↑↑
Male aggression	?	↑	←→	?
Female aggression	↑↑ or ↓	?	↓↓	?

Levels of increase are indicated by ↑ and decreases by ↓; ←→ indicates no change; - indicates behaviour not shown; ? indicates not tested. For references, see text.

maternal responsiveness to occur optimally. Indeed, this is further supported by observations in the rat that oxytocin antagonist infusions into these regions inhibited some, but not all, components of maternal behaviour. Also, effects of oxytocin antagonist on crouching behaviour were more pronounced when it was infused in the medial preoptic area (Pedersen *et al.* 1994). Similarly oxytocin infusions into the rat olfactory bulb, while inducing most aspects of maternal behaviour, failed to influence nest building (Yu *et al.* 1996*a*).

Predicted effects of oxytocin infusions in other terminal regions

Behavioural effects of oxytocin infusions have not been investigated in a number of the terminal projection regions featured in Fig. 2. The most likely role for oxytocin release within the substantia nigra would be to promote immobilization responses, which are important for acceptance of suckling. While no studies have yet investigated the effects of oxytocin infusions into the lateral septum and cingulate cortex, they may specifically influence positive maternal behaviour components. However, a possibility remains that non-primate mammals do not spontaneously exhibit maternal behaviour because it is under constant inhibitory control and that the main function of oxytocin release at birth is to remove this inhibition and allow maternal responses to be expressed.

Neural sites of oxytocin actions on social behaviour

Unfortunately, no studies have yet examined the effects of localized infusions of oxytocin on female bonding behaviour in prairie voles although it would seem likely that it would involve a similar distributed action at a number of different brain sites, since olfactory memory, reward mechanisms and social behaviours are all involved

How does vagino-cervical stimulation activate oxytocinergic systems?

Classical neurotransmitter systems, neuropeptides, steroid hormones and maternal experience all potentially influence the ability of vagino-cervical stimulation (VCS) to activate PVN oxytocinergic neurones.

Influence of classical transmitter systems on PVN neurones

The effects of VCS on the brain are relayed primarily through the pelvic and vagal nerves, spinal cord and brainstem nuclei to the hypothalamus (Guevera-Guzman *et al.* 1999). While we still do not know precisely which neurotransmitter pathways to the PVN are responsible for stimulating maternal behaviour through altering PVN neurone activity, the main candidates are summarized in Fig. 2. Glutamate, GABA, noradrenaline (NA), 5-hydroxytryptamine (5-HT) and dopamine concentrations all increase significantly in the PVN during parturition when oxytocin concentrations are also increased (see Table 1). Noradrenaline derived from A1, A2 and A6 projections from the brainstem is known to stimulate the activity of oxytocinergic neurones (Randle *et al.* 1986) and, in the rat, parturition and VCS activate these cell groups (Luckman, 1995). The main dopaminergic projection to the PVN comes from the A10 cell group in the ventral tegmentum and dopamine has been shown to have an excitatory action on oxytocinergic magnocellular neurons in the PVN (Moos & Richard, 1982). In rats, 6-hydroxydopamine lesions of the ventral tegmental area disrupt maternal behaviour (Hansen *et al.* 1991), so it is possible that this dopaminergic projection is important in mediating parturition-induced activation of the parvocellular oxytocin neurones in the PVN. The 5-HT inputs to the PVN from the dorsal raphé nucleus have been implicated in both inhibitory (Moss *et al.* 1972) and excitatory effects (Saphier, 1991) on oxytocinergic neurones. Recent evidence has also suggested that serotonin re-uptake inhibitors facilitate plasma oxytocin release and that the anxiolytic and anti-depressive effects of these agents might even be partially mediated via oxytocin (Uvnäs-Moberg *et al.* 1999). Altered patterns of glutamate and GABA release in the PVN may also modulate PVN oxytocinergic cells since they are strongly innervated by glutamate terminals, and oxytocin release can be evoked by an AMPA/kainate receptor agonist (Parker & Crowley, 1993). Glutamate may further act in concert with NA, since combined treatment with an α_1-agonist and AMPA produce synergistic effects on oxytocin cell discharges (Parker & Crowley, 1993). GABA release from local interneurones

Table 2. Brain regions demonstrating increased *c-fos* expression during birth or vagino-cervical stimulation and containing oxytocinergic cells, projections or receptors

	c-fos mRNA expression*				Receptors	
Brain regions	**Birth + Lamb**	**VCS alone**	**Oxytocin cells**	**Projections**	**Rat**	**Sheep**
Hypothalamus						
mediobasal	++	++	+	++	+++	++
medial preoptic area	++++	++++	+++	++	+++	++
paraventricular nucleus	++	++	+++	+++	++	++
supraoptic nucleus	++++	++++	++	+++	++	++
periventricular complex	+++	+++	++	++	++	++
arcuate nucleus	nr	nr	-ve	-ve	-ve	++
Olfactory system						
olfactory bulb	+	+	-ve	+	+	++
islands of Calleja	nr	nr	-ve	nr	-ve	+++
olfactory tubercle	nr	nr	-ve	nr	+++	+
pyriform cortex	+++	-ve	-ve	++	++	++
endopyriform nucleus	nr	nr	-ve	nr	-ve	++++
Association cortex						
medial frontal cortex	+	+	-ve	+	+	+
anterior cingulate	++	+	-ve	+	+	++
posterior cingulate	++	+	-ve	nr	nr	++
insular cortex	nr	nr	-ve	nr	nr	+++
taenia tecta	nr	nr	-ve	nr	nr	+
parietal cortex	nr	nr	-ve	nr	nr	+
temporal cortex	nr	nr	-ve	nr	nr	+
insular cortex	nr	nr	-ve	nr	++	++
Limbic system						
diagonal band	nr	nr	-ve	+	+	++
lateral septum	+++	++++	-ve	++	+++	++
bed nucleus stria terminalis	+	+++	++	+	+++	++
amygdala	+++	+++	-ve	++	+++	+
hippocampus CA1-4	+++	++	-ve	nr	+++	+++
subiculum	++	nr	-ve	nr	+++	+++
Basal ganglia						
nucleus accumbens	nr	nr	-ve	+	+	+
substantia nigra	nr	nr	-ve	nr	-ve	-ve
Thalamus and epithalamus						
mediodorsal thalamus	++	++	-	nr	-ve	-ve
habenula	++	++	-ve	nr	-ve	-ve
Brain stem structures						
central grey	nr	nr	-ve	nr	+	++
raphe nucleus	nr	nr	-ve	nr	+	-ve
reticular nucleus	nr	nr	-ve	nr	+	++
inferior olive	nr	nr	-ve	nr	+	++
tractus nucleus solitarius	nr	nr	-ve	nr	-ve	-ve
vestibular nuclei	nr	nr	-ve	nr	+	+

+, ++, +++ and ++++ indicate low, medium, high and very high levels; nr, not recorded; –ve, not found. Data derived from Broad *et al.* 1993*a*, 1999; Yoshimura *et al.* 1993; da Costa *et al.* 1997. *From studies on sheep.

may also modulate the activity of oxytocinergic neurones through inhibitory feedback.

Influence of neuropeptide systems on PVN neurones

Neuropeptides, in addition to classical transmitters, can also modulate the activity of PVN oxytocinergic cells including auto-excitation by oxytocin itself. In both sheep and rats, once oxytocin is released within the PVN, it can promote activity of the oxytocinergic neurons to stimulate further oxytocin release in a short-loop feedback (Moos *et al.* 1984; da Costa *et al.* 1996). This may explain why increased concentrations in the brain at birth can often last for 1–2 h post-partum. This prolonged release maximizes the chance that maternal responses will be reliably stimulated in response to offspring,

Table 3. Brain oxytocin and classical transmitter release assoicaited with the inducation of maternal behaviour by birth or vagino-cervical stimulation

Brain region	OT	GLU	GABA	NA	DA	5-HT	ACh
BNST (sheep)	↑	↑	↑	↑	↓	↑	?
MBH (sheep)	↑	↔	↑	↑	?	?	?
MPOA (sheep)	↑	↑	↑	↑	↑	?	?
PVN (rat & sheep)	↑	↑	↑	↑	↑	↑	?
supraoptic nucleus (rat)	↑	?	?	?	?	?	?
olfactory bulb (sheep)	↑	↑	↑	↑	↑	?	↑
hippocampus (rat)	↑	?	?	?	?	?	?
septum (rat & sheep)	↑	↑	↑	↑	↑	↑	↑
substantia nigra (sheep)	↑	?	?	↑	?	?	?

Concentration increases are indicated by ↑ and decreases by ↓; ⟷ indicates no change; ? indicates not tested. BNST, bed nucleaus of stria terminalis; MBH, mediobasal hypothalamus; MPOA, medial preoptic area; PVN, paraventricular nucleus; OT, oxytocin; GLU, glutamate; 5-HT, 5-hydroxytryptamine; NA, noradrenaline; DA dopamine; ACh, acetylcholine. For references, see text.

even if an individual animal has had a difficult birth and is slow to recover, or if it becomes temporarily separated from its offspring. There is also evidence that endogenous opioids and corticotropin-releasing hormone (CRH) may have a modulatory role in mediating the post-partum induction of maternal behaviour in sheep. Both morphine and CRH given I.C.V. facilitate VCS induction of maternal behaviour and central oxytocin release in sheep (Keverne & Kendrick, 1991). On the other hand, treatment with the opioid antagonist naltrexone reduces VCS-induced maternal behaviour and oxytocin release (Kendrick & Keverne, 1989) and interferes with post-partum induction of maternal behaviour (Caba *et al.* 1995). Levels of both pre-proenkephalin and CRH mRNA are increased in the PVN of sheep at parturition (Broad *et al.* 1993*b*, 1995), further suggesting an enhanced modulatory role for opioid and CRH activity when maternal behaviour is expressed. A similar facilitatory role for endogenous opioids in the control of maternal and social affiliative behaviours has been shown in the rhesus monkey (Martel *et al.* 1993). However, in the rat, inhibitory actions of opioids on maternal behaviour and oxytocin release have been reported (Bicknell *et al.* 1988; Bridges, 1990), even though concentrations of β-endorphin are increased in the hypothalamus at parturition (Wardlaw & Frantz, 1983).

Influence of steroid hormones and maternal experience

Other factors which influence the ability of VCS to stimulate brain oxytocin release are sex hormones and maternal experience. This would obviously be predicted from neuroanatomical data showing that they influence expression levels of oxytocin and its receptor. Thus oestrogen alone, or in combination with progesterone, facilitates VCS-induced release of the peptide in the mediobasal hypothalamus of sheep (Kendrick *et al.* 1993). Progesterone has also been shown to directly stimulate oxytocin release in the rat preoptic area (Caldwell *et al.* 1992). In sheep, the ability of birth to evoke oxytocin and classical transmitter release within the olfactory bulb is significantly enhanced in maternally experienced animals compared with inexperienced counterparts (Keverne *et al.* 1993; Lévy *et al.* 1995).

How does oxytocin release at different neural sites promote its behavioural actions?

The central question that needs to be answered is how co-ordinated oxytocin release within the brain acts to promote maternal behaviour and social behaviours? Does the peptide simply act upon its receptor(s) to alter the electrical activity of cells or does it indirectly modulate the activity of other neurotransmitter systems?

Are oxytocin's actions on behaviour mediated directly or indirectly?

Two observations immediately suggest that oxytocin mainly alters maternal behaviour through indirect rather than direct actions. In the first instance we know that oxytocin is not important for maintaining maternal behaviour once it is established and is not essential for maternal behaviour induction following prolonged exposure to young. Thus, other factors must play the key role in these circumstances. Secondly, similar patterns of classical transmitter release in oxytocin terminal regions are seen during parturition or in response to VCS (Table 3) and many of these are known to be important for the expression of maternal behaviour. Indeed, the remarkable similarity in patterns of classical transmitter release in oxytocin terminal regions suggests that it is being co-ordinated in some way. In sheep, oxytocin infusion by retrodialysis at doses that influence components of maternal behaviour, increases noradrenaline release in the olfactory bulb, mediobasal hypothalamus, medial preoptic area and PVN, GABA release in the medial preoptic area and olfactory bulb, dopamine release in the PVN and acetylcholine release in the olfactory bulb (Kendrick *et al.* 1992*a*, 1993; Lévy *et al.* 1995; da Costa *et* *al.* 1996). These actions must presumably be mediated by oxytocin receptors located on the terminals of the aminergic neurones. Noradrenaline, dopamine and GABA have all been implicated in the control of maternal behaviour in rodents (Hansen *et al.* 1991; Numan, 1994) and oxytocin may partly induce maternal behaviour by facilitating release of these transmitters within the neural substrates specifically involved in its control.

The possibility that many of oxytocin's behavioural actions may be mediated by facilitating classical transmitter release, has recently received support from work in rats showing that enhancement of olfactory social recognition memory by oxytocin is dependent on noradrenaline (Dluzen *et al.* 1998). Plasticity changes in the olfactory bulb associated with memory formation are triggered by the release of noradrenaline that follows VCS (Lévy *et al.* 1993). In sheep, noradrenaline acts via β-noradrenergic receptors to reduce the activity of the GABAergic granule cells. This in turn dis-inhibits the glutamatergic mitral cells, which are also activated by the specific lamb odour that is being learned, and the resultant glutamate release stimulates nitric oxide production leading to a cyclic GMP-dependent facilitation of further glutamate release. This facilitation then leads to protein-dependent changes which permanently upregulate the sensitivity of mitral-to-granule cell synapses activated by the learned odour (see Kendrick *et al.* 1997*b*). Thus, the presence of oxytocin receptors on the noradrenergic terminals ensures that birth- or VCS-induced release of noradrenaline is enhanced and thereby facilitates the above effects. However, the release of oxytocin is clearly not essential for learning because VCS directly excites the noradrenergic projections. However, direct infusion of oxytocin can bypass the necessity for the noradrenergic projections to the olfactory bulb to be excited by VCS since it can promote noradrenaline release through a presynaptic action.

Similarly in voles, it has recently been shown that the mating-induced development of partner preference in female prairie voles can be prevented by blockade of D2 dopamine receptors in the nucleus accumbens (Wang *et al.* 1999). While we presently only have evidence that oxytocin can release dopamine in the PVN (da Costa *et al.* 1996), it seems possible that oxytocin release in dopaminergic projection regions, such as the substantia nigra, ventral tegmentum and nucleus accumbens, influences behaviour by facilitating dopamine release.

One final issue that bears consideration in this model is how the feedback loop of oxytocin facilitating its own release is terminated? Certainly neither oxytocin concentrations nor those of classical transmitters remain permanently elevated in any brain region for more than an hour or so post-partum. The easiest answer to this is that either brain oxytocin levels become depleted or that oxytocin receptors become desensitized. Infusions of oxytocin into the PVN inhibit glutamate and aspartate release after an hour or more (da Costa *et al.* 1996) and this may indicate a downregulatory action of the peptide on its own synthesis and possibly that of its receptor. Indeed in rats, oxytocin mRNA expression is downregulated shortly after parturition (Crowley *et al.* 1995). In sheep, behavioural responses to PVN oxytocin infusions separated by 1 h are also reduced, suggesting that some receptor desensitization can occur as well (da Costa *et al.* 1996).

Thus, we have a simple explanation for why oxytocin release, and the PVN itself, are important for facilitating maternal behaviour induction (and probably for the stimulation of other social behaviours) but not for its expression or maintenance. The direct mediators of such behaviours are the classical transmitter systems and their receptors and these can operate independently of the PVN and oxytocin. However, evolution has provided a fast-track facilitatory system for induction of these responses under conditions where speed, reliability and specificity of altered behavioural priorities is important (i.e. recognizing, nurturing and bonding with young or recognizing and bonding with a mate). Thus oxytocin release can selectively enhance the levels of classical transmitter released in the specific regions mediating appropriate behavioural responses. Once behavioural changes are established, however, there is no need for this facilitatory system to have continued involvement and the PVN is not essential for the ability of relevant stimuli to promote further classical transmitter release. Equally, this is only a 'kick-start' system and sufficient activation of classical transmitter systems can occur in the absence of oxytocin to promote maternal and social behaviours, albeit more slowly and possibly with a reduced degree of specificity.

Why are there species differences in the importance of oxytocin for maternal behaviour?

While differences in patterns of oxytocin receptor expression may explain different species effects of oxytocin on social bonding behaviours (Insel & Shapiro, 1992), it is less easy to point to clear receptor differences that might explain why the peptide is more effective at stimulating maternal behaviour in some species than in others. It is possible that there may be species variations in oxytocin's potency for mediating classical transmitter release. There may also be species differences in the level of brain oxytocin release that is evoked by giving birth. For example, in precocial species like sheep, which give birth to a small number of large, well developed young, the level of vaginal, cervical and uterine stimulation associated with birth is high compared with altricial species like rats and mice which give birth to large numbers of small undeveloped young. Therefore in altricial species other factors not specifically related to the birth process (such as sex steroids and prolactin) itself might be required to play a greater role.

Is this proposed indirect mode of action on behaviour unique to oxytocin?

This proposed model of how oxytocin acts to influence behaviour may be more generally applied to other neuropeptide systems. Many neuropeptides have now been reported to modulate classical transmitter release (Guevara-Guzman *et al.* 1993; Lévy *et al.* 1995; Hathway *et al.* 1998). This raises the possibility that specificity of behavioural actions in the diffuse transmitter systems may be contributed to by their being differentially modulated by neuropeptide systems that have more limited distributions within the brain. This idea helps explain how classical transmitters with their widely distributed brain projections can influence so many different and often conflicting behaviours at different times. The idea that a neuropeptide, with a more limited distribution within the brain, could act to potentiate classical transmitter release in just a restricted number of brain regions mediating a specific behaviour is an attractive solution to this. Furthermore, it suggests that neuropeptide systems offer important therapeutic targets for more selective treatments of behavioural and social dysfunctions where current treatments target the diffuse transmitter systems and their receptors and may therefore produce unwanted side effects.

Future questions

The proposed model for oxytocin's actions on behaviour clearly needs further research to determine specific effects of the peptide at various brain sites and the dependence of these on modulation of classical transmitter systems. In view of increasing evidence for differential behavioural effects of the peptide across species, dependent upon receptor localization and expression levels, the question also arises as to whether behavioural dysfunctions within species can be attributed to altered receptor activity.

While the role of brain oxytocin release in humans is still a matter for some speculation, a number of studies have correlated behavioural and mood changes with blood concentrations of the peptide. Recent work has also indicated that blood levels are significantly reduced in autism and type II schizophrenia which are associated with dysfunctions in social behaviour (Modahl *et al.* 1998; Insel *et al.* 1999). Similarly, evidence has linked the anti-depressant, anxiolytic actions of serotonin re-uptake inhibitors (SSRI's) with modulation of oxytocin secretion (Uvnäs-Moberg *et al.* 1999). Even though such findings are based on measurements of peripheral oxytocin release, which are not a reliable guide to changes within the brain, there is clearly a possibility that this peptide does have some role in regulating social and emotional behaviours in humans, and more work is needed to investigate this.

Finally, the brain oxytocinergic system does offer a potential therapeutic target for dysfunctional social behaviour, and we will need to develop new pharmacological agents which can influence the brain, as opposed to peripheral organs.While the role of oxytocin in parturition and milk ejection has been established for a considerable time, the potential for its release within the brain to influence behaviour was not demonstrated until 1979 when it was shown to induce maternal behaviour in non-pregnant rats (Pedersen & Prange, 1979). It was not until 1986, however, that detailed evidence was produced in sheep that brain oxytocin levels are elevated by vagino-cervical stimulation occurring at the time of birth (Kendrick *et al.* 1986). Since that time the peptide has also been associated with influences on social, sexual and aggressive behaviours and even in memory function (Table 1). This review will consider how oxytocin acts to produce such behavioural effects, concentrating mainly on maternal and social bonding actions where most experimental data exist.

Neuroanatomical localization of oxytocin and its receptors

Immunocytochemistry and *in situ* hybridization histochemistry have revealed that the distribution of cells and processes containing oxytocin immunoreactivity or mRNA is broadly similar in many species (Sofroniew, 1983; Broad *et al.* 1993*a*; Crowley *et al.* 1995).

The major source of oxytocin neurones that project within the brain is the hypothalamic paraventricular nucleus (PVN).

There is similar agreement across species about the regions that contain cells expressing oxytocin receptor mRNA (Yoshimura *et al.* 1993; Broad *et al.* 1999), although this has only become established with the cloning and sequencing of the receptor gene, allowing mRNA expression to be detected. Studies using ligand binding have not always been successful in demonstrating the presence of these receptors in some species (Lévy *et al.* 1992*a*; Tolockzo *et al.* 1997). Recent studies quantifying changes in mRNA expression or protein have overcome this problem and indicated that distribution within the brain is far more extensive than originally thought (Broad *et al.* 1999; Table 2). There is a remarkable concordance between brain sites showing increased *c-fos* mRNA expression (used as an activity-dependent marker) following the induction of maternal behaviour and those containing oxytocinergic cells, processes and receptors (da Costa *et al.* 1997; Kendrick *et al.* 1997*a*; Table 2). This is also the case for structures important in mediating social and sexual behaviours and social recognition/bonding based on olfactory cues (Flanagan *et al.* 1993; da Costa *et al.* 1997).

Factors which influence the potential for an animal to show maternal or socio-sexual behaviours also impact on the levels of oxytocin and oxytocin receptor expression in a number of different species. Thus, levels of oxytocin immunoreactivity, mRNA expression and receptor mRNA expression are altered in many regions associated with maternal behaviour at the time of parturition, during lactation and following exogenous treatments with oestrogen and progesterone (Burbach & Adan, 1990; Insel & Shapiro, 1992; Schumacher *et al.* 1992; Broad *et al.* 1993*a*; Crowley *et al.* 1995; Zingg *et al.* 1995). Similarly, differential levels of oxytocin receptor expression are seen in the bed nucleus of the stria terminalis, lateral septum and nucleus accumbens in mouse and vole strains depending upon whether they have a social/monogamous disposition or an asocial/promiscuous one (Insel *et al.* 1991; Insel & Shapiro, 1992). These regions are known to be important for social behaviours and their associated rewards.

In rats, oxytocinergic cells do not have large numbers of oestrogen receptors (Burbach *et al.* 1995) and of these only the β-type is expressed (Patisaul *et al.* 1999). Also, although the rat oxytocin gene does have a putative oestrogen responsive element, it is imperfect (Burbach & Adan, 1990) and does not appear to have an important role *in vivo*. Indeed in sheep, upregulation of mRNAs for both oxytocin (Broad *et al.* 1993*a*) and its receptor (Broad *et al.* 1999) in PVN cells as a result of pregnancy is not entirely mimicked by oestrogen and progesterone treatment. Therefore other factors, such as glucocorticoids or thyroid hormone, may contribute to the stimulation of the oxytocin peptide and receptor genes (Adan *et al.* 1993).

Another important factor that influences levels of oxytocin receptor mRNA expression is maternal experience. In sheep, nulliparous ewes are known to have more problems in developing post-partum maternal responses than multiparous ones. The level of birth-induced upregulation of oxytocin receptor mRNA in the PVN of primiparous ewes is significantly less than that seen in multiparous ones (Broad *et al.* 1999). Interestingly, work in rats has also shown that maternal experience can induce permanent morphological changes in oxytocinergic neurones (Hatton *et al.* 1992).

As already discussed, c-*fos* expression is increased in oxytocinergic cells at the time of birth when oxytocin and its receptor are also upregulated. Mutant mice lacking the *fos*-b gene, another member of the Fos family, show defective nursing behaviour (Brown *et al.* 1996). We have recently shown that c-*fos*/c-*jun* antisense infusions into the PVN prevent upregulation of oxytocin expression at birth and impair oxytocin release and some aspects of maternal behaviour (da Costa *et al.* 1999). Thus this immediate early gene family may exert an important transcriptional control over the expression of the oxytocin gene in the PVN.

Oxytocin and maternal behaviour

Behavioural effects of oxytocin and oxytocin antagonists

It was first demonstrated in rats that intracerebroventricular (I.C.V.) infusions of oxytocin can induce short-latency (< 30 min) maternal responses in hormone-primed virgin animals (Pedersen & Prange, 1979; Pedersen *et al.* 1982; Fahrbach *et al.* 1985*a*). Infusions of the related peptide vasopressin were considerably less effective in this respect. Later experiments showed that I.C.V. infusions of oxytocin antagonists (van Leengoed *et al.* 1978; Fahrbach *et al.* 1985*b*) or antisera (Pedersen *et al.* 1985) could prevent these actions of oxytocin, and could also delay the onset of post-partum maternal behaviour. This led to the attractive hypothesis that oxytocin could have complementary actions in terms of its peripheral and central actions. On the one hand it could promote uterine contractions and milk let-down peripherally, and promote maternal responsiveness by acting centrally. Similar complementary peripheral and central actions have been claimed for other peptides such as angiotensin, cholecystokinin, corticotropin-releasing hormone, luteinizing hormone-releasing hormone and vasopressin. However, while similar effects of I.C.V. infusions were later reported in mice (McCarthy, 1990), the precise importance of central oxytocin release in maternal behaviour induction in rodents has been called into question. Thus some groups failed to find any effects of I.C.V. oxytocin in rats (Rubin *et al.* 1983; Bolwerk & Swanson, 1984) or could only obtain them in anosmic animals or animals in novel environments (Wamboldt & Insel, 1987). The most recent negative evidence comes from mice with a targeted mutation of the oxytocin gene which have no reported dysfunction in maternal behaviour (Nishimori *et al.* 1996; Young *et al.* 1997).

These varied findings in both rats and mice are perhaps not that suprising in view of the fact that oxytocin infusions do not mimic the speed of induction of maternal behaviour seen post-partum (i.e. it takes > 30 min for I.C.V. infusions of oxytocin to have behavioural effects whereas these behaviours are induced immediately post-partum). Further, the mouse strain used to make the oxytocin gene knockout (C57Bl6) is almost spontaneously maternal when presented with pups (Young *et al.* 1997). Indeed, in both mice and rats the mere presence of pups reliably evokes maternal responses after treatments with sex hormones, and is independent of the process of actually giving birth. Thus, if brain oxytocin release plays a role in the control of maternal behaviour in these species, it is a facilitatory rather than an essential one.

One other point that is clear from rodent studies is that if the main source of brain oxytocin projections, the PVN, is damaged then post-partum induction of maternal behaviour is delayed, but once maternal behaviour is established then damage to this region does not interfere with it. This has been shown both using lesions in rats (Insel & Harbaugh, 1989) and indirectly in mice mutant for the imprinted gene PEG3, where deficits in post-partum maternal behaviour induction are correlated with significant cell loss in the PVN (Li *et al.* 1999).

In sheep, evidence suggests that oxytocin plays a much greater role in post-partum induction of maternal responses. Intracerebroventricular oxytocin infusions can induce full maternal responses in < 30 s in non-pregnant animals, provided that they are oestrogen-primed (Kendrick *et al.* 1987). None of the oxytocin receptor antagonist ligands used to block oxytocin effects in rodents have proved to be effective in sheep and indeed cannot be used to demonstrate receptor binding in sheep brain (although they do bind in the kidney) (Lévy *et al.* 1992*a*). However, oxytocin actions can be partially blocked by infusions of the cyclic hexapeptide receptor antagonist L-366,670 (Fig. 1). The oxytocin receptor agonist Thr^4,Gly^7-oxytocin is just as potent as oxytocin in stimulating maternal behaviour. Similar infusions of up to 50 μg of vasopressin have no significant effect.

In sheep, maternal experience also influences responsivity to oxytocin, as would be predicted from findings on oxytocin receptor mRNA expression. Thus, with short-term progesterone and oestrogen priming, I.C.V. oxytocin fails to reliably induce full maternal behaviour in nulliparous ewes but is effective in multiparous ones (Keverne & Kendrick, 1991). However, in nulliparous animals exposed to long-term combined sex steroid treatment (i.e. 6–8 weeks, which is sufficient to stimulate lactation; Kendrick *et al.* 1992*a*), I.C.V. oxytocin is effective in stimulating full maternal behaviour (K. M. Kendrick, unpublished observations). Similarly in primiparous ewes prevented from becoming maternal at birth by using an epidural anaesthetic block, I.C.V. oxytocin treatment was also effective in inducing full maternal responsiveness (Lévy *et al.* 1992*b*).

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